

REMARKS

In the Office Action dated 6/15/2005, the Examiner rejected claims 1-40 as being unpatentable under 35 USC §102(b) and 35 USC §103(a). By this communication, claims 1,2, 4, 6, 19, 20, 21, 24, and 39 - 40 have been amended to more clearly define the invention. Claims 1-40 are still pending. Applicant respectfully requests reconsideration of the application in view of the foregoing amendments and the remarks set forth below.

Rejections Under 35 USC §102(b)

Rejections Based on Buckley

Claims 1, 2, 8 and 15-22 were rejected under 35 USC §102(b) as being clearly anticipated by Buckley (US Patent No. 5,463,219). Applicant submits that each of the rejected claims as amended recites at least one element that is not disclosed or suggested by Buckley, and that the §102(b) rejection should consequently be withdrawn.

Claim 1, as amended, recites a method of operating a mass spectrometer, the mass spectrometer including a source of ions, a mass analyzer and a detector, wherein the method includes a step of calculating a gain of the detector **directly from** intensity measurements for ions having a plurality of different m/z (mass to charge ratio) values. This limitation is not taught or suggest by the Buckley reference.

Exemplary implementations of this step involve the application of equations that appear at (among other places) page 14, paragraph [0053], page 15, paragraph [0055] and page 16, paragraph [0058]. As stated, embodiments of the current invention practice a method in which the ion beam intensity at two or more distinct mass-to-charge ratio values are measured, the two values being taken under conditions such that the two values of mass-to-charge ratio have the same contribution from other sources of variation. From these two or more intensity values, the gain of the detector is directly calculated, and hence any contribution from the unstable source can be eliminated.

In setting forth the rejection of claim 1, the Examiner has stated that Buckley teaches the gain of the detector to be determined from the slopes of a series of curves that are of analog

intensity on the vertical axis and pulse counts on the horizontal axis. Also stated was that the resultant gain values are plotted against mass to yield a gain curve, and from the gain curve, the instrument can determine the relationship between gains and masses at positions between the measured points. A review of the Buckley patent, including the cited sections thereof, do not reveal any teachings regarding the calculation of the gain of the detector **directly from** the variance of signal intensities of ions for a plurality of different mass-to-charge ratios.

Buckley teaches a calibration procedure in which, during calibration for one substance, which is effectively one mass-to-charge ratio, the analog intensity is plotted on the vertical axis, and the number of ions hitting the detector on the horizontal axis. From this plot, the gain for this one substance can be calculated using the pulse count and the analog intensity signal. A plot is made of the analog intensity measured against pulse counts for different substances, that is for different mass-to-charge ratios. From each plot, a different gain can be determined, each gain being determined from the slope of a particular m/z ratio. Buckley then goes on to describe (starting at column 16, line 56) that the resultant gain values are then plotted against mass. Buckley does not teach or suggest how a **direct** relationship between gain and intensity of a **plurality** of mass-to-charge ratios can be used to calculate a gain of a detector. Instead, Buckley teaches that several steps are required to calculate the gain. The first gain calculation is based on ion intensity measurements of **one** mass-to-charge ratio. The gain results are then used to create a gain curve, and from this gain curve, subsequent gains can be determined for any mass, but not **directly from** any ion intensity measurements from a **plurality** of mass-to-charge ratios, but only indirectly therefrom. In other words, the direct calculation limitation set forth in amended claim 1 distinguishes the claimed subject matter from techniques, such as that taught in Buckley, where at least one intervening step must be executed between the acquisition of intensity measurements and the calculation of gain.

Claims 2, 8 and 15-18 depend directly from claim 1 and inherit all the limitations thereof, and are submitted to be patentable over Buckley for at least the reasons advanced above in connection with Claim 1.

In light of the above discussion, applicant submits that Claims 1, 2, 8, and 15-18 as amended are patentable over Buckley, and withdrawal of the §102(b) rejection is therefore respectfully requested.

Claims 19-21, as amended, recite elements substantially similar to claim 1, and are submitted to be patentable over Buckley for substantially the same reasons advanced above in connection with claim 1. More specifically, claim 19 is directed to a mass spectrometer including a source of ions, a mass analyzer configured to accumulate ions, a detector and a control means operable to calculate a gain of the detector directly from intensity measurements for ions having a plurality of different m/z (mass to charge ratio) values. Claim 20, is directed to a computer program product including the step of calculating a gain of the detector directly from intensity measurements for ions having a plurality of different m/z values. Claim 21 is directed to a method of operating a mass spectrometer, the mass spectrometer including a source of ions, a mass analyzer and a detector; the method comprising calculating the number of ions directly from intensity measurements for ions having a plurality of different m/z (mass to charge ratio) values. As discussed above, Buckley fails to teach or suggest the calculation of gain or the number of ions being achievable **directly from** the intensity measurement of **a plurality of** different m/z values.

Claim 22 depends directly from claim 21 and inherits all the limitations thereof, and is submitted to be patentable over Buckley for at least the reasons advanced above in connection with Claim 21.

In light of the above discussion, applicant submits that Claims 19-22 as amended are patentable over Buckley, and withdrawal of the §102(b) rejection is therefore respectfully requested.

Rejections Under 35 USC §103(a)

Rejections Based on Buckley in view of Shimomura

Claims 3-7, 9-13, 23-33, and 35-40 were rejected under §103(a) as being unpatentable over Buckley in view of Shimomura (U.S. Patent No. 6,265,714). Applicant traverses these rejections as applied to the amended claims.

In setting forth the rejection of claims 3-7, 23-28, 39 and 40 the Examiner has stated that Buckley discloses nearly all the limitations of claims 3-7, 23-28, 39 and 40, but fails to teach calculating gain or number of ions based on formulas. The Examiner goes on to state that Shimomura discloses the reading of intensity data, and obtains therefrom the average intensity and standard deviation, as well as their ratio, these numbers serving to determine detector degradation.

Shimomura teaches the use of the ratio of the average intensity to standard deviation, called the deviation-to-average ratio, in order to look for a **change** in the gain, which is an indication of detector degradation, and to assess whether his detector degradation measurement is being affected by some other process. Shimomura is concerned with the **change** in the gain, not the gain itself. Nothing in Shimomura teaches or suggests that his process can be used to calculate the gain itself, and does not teach or suggest that his process can be used to calculate an absolute gain measurement.

Claims 3-7 depend directly or indirectly from amended claim 1, and inherit all the limitations thereof. Claims 23-28, 39 and 40 depend directly or indirectly from amended claim 21, and inherit all the limitations thereof. In addition, as can be seen from the equations described in the application, the gain can **not** be obtained using the deviation-to-average ratio as an input value. This can be seen particularly in claims 3-7, 23-28.

Furthermore, as described by Shimomura is column 2, lines 49-65, and in the example given in Shimomura column 4, Table 1, and lines 3-8, if the average intensity of the detector decreases with time but hardly any change is observed in the deviation-to-average ratio, i.e. it is constant, the conclusion is that the lowering of the intensity value is due to the degradation of the detector itself. The current invention teaches against the assumption that the deviation-to-average ratio is constant as the detector degrades. In contrast, the Applicant states on page 12, paragraph [0046] that Poisson statistics dictates the variance, σ_N^2 , is directly related to the number of ions detected, so it is the deviation squared-to-signal ratio that is constant.

Assuming that the teaching of Buckley and Shimomura may be properly combined, modifying Buckley to include the use of the standard deviation method of Shimomura, such a

combination would still not provide a method for calculating the absolute gain or the number of ions detected directly from the intensity measurements for ions having a plurality of different m/z values. Instead the references would yield a method of determining if the detector had degraded based on formulae that contradict the assumptions of the current application. Moreover it would not be obvious to modify the Buckley method to utilize the Shimomura formulae, since Shimomura is based on formulae that contradict the assumptions of the current application. Moreover, because neither of the references, either taken alone or individually, teaches or suggests the limitation recited in claim 1 of the gain or the number of ions being achievable **directly from** the intensity measurement of **a plurality** of different m/z values, the §103(a) rejection based on these references should be withdrawn.

Furthermore, the Examiner relies on Buckley for the teaching of a temporally unstable source of ions, stating that this limitation is found in claims 9-13, 31-33 and 36. Applicant if unable to find this limitation in claims 10, 12, 13, 32, 33, or 36.

In setting forth the rejection of claims 9-13, 31-33, and 36, the Examiner has stated that Buckley describes source 12, as used in French *et al.* which is an unstable atmospheric ion source. The ion source used by Buckley and French is described as one which experiences signal drift (French, column 1, line 48) which is characterized by a change in signal over a long period of time (French, column 1, lines 30-33).

The temporally unstable source of ions is discussed in the specification at (among other places) page 3, paragraph 0011. Briefly described, the temporally unstable sources discussed by the Applicant may be ones which experience signal variation over extremely short periods of time, from one scan to another, due to characteristics such as viscosity and ionic strength, for example, and are not limited to signal drift.

Neither of the references, either taken alone or individually, teaches or suggests the limitation to temporal instability of the ion source, and the §103(a) rejection based on these references should be withdrawn.

Rejections Based on Buckley in View of Shimomura and Kammei

Claim 14 and 34 were rejected under §103(a) as being unpatentable over Buckley in view of Shimomura, and further in view of Kammei (US Patent No. 6,674,068). Applicant traverses these rejections as applied to the amended claims.

Claim 14 depends directly from claim 1 and inherits all the limitations thereof, and is submitted to be patentable over Buckley for at least the reasons advanced above in connection with Claim 1. Claim 34 depends directly from claim 21 and inherits all the limitations thereof, and is submitted to be patentable over Buckley for at least the reasons advanced above in connection with Claim 21. None of the aforementioned references teaches a step of calculating gain directly from intensity measurements obtained for ions having a plurality of different mass-to-charge ratios. Therefore the §103(a) rejection based on these references should be withdrawn.

In view of the above discussion, it is submitted that the Application is now in condition for allowance and such favorable action is respectfully requested. The Examiner is invited to contact the undersigned Applicant's representative by telephone if he believes that doing so will be helpful to resolve any outstanding issues and advance the prosecution of the Application.

Applicant hereby authorizes the Commissioner to charge Deposit Account No. 50-3267 the amount of \$600 for payment of the additional independent claims. It is believed that no other fee is due however the Commissioner is hereby authorized to charge any fees which may be required, or to credit any overpayment, to Deposit Account No. 50-3267.

Respectfully submitted,

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